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PHASE 3 SUMMARY OF MRID 00094002:

ACUTE INHALATION TOXICITY IN THE RAT

STUDY # 420-0703

FLUMETRALIN

GUIDELINE REFERENCE:

81-3 ACUTE INHALATION TOXICITY IN THE RAT

SUMMARY PREPARED BY:

JACQUELINE GILLIS, Ph.D.

MERRILL TISDEL

14 SEPTEMBER 1990

ORIGINAL STUDY PREPARED BY:

TOXIGENICS, INC.

DECATUR, ILLINOIS

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STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA §10(d)(1)(A), (B), or (C).

Company: CIBA-GEIGY Corporation (Typed Name)

Company Agent: Thomas Parshley (Typed Name)

Title: Senior Reg. Specialist

Signature: _____ Date: _____

These data are the property of the Agricultural Division of CIBA-GEIGY Corporation, and as such, are considered to be confidential for all purposes other than compliance with FIFRA §10. Submission of these data in compliance with FIFRA does not constitute a waiver of any right to confidentiality which may exist under any other statute or in any other country.

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GOOD LABORATORY PRACTICE STATEMENT

ToxiGenics, Inc., is no longer in business. Therefore, a GLP statement cannot be obtained from a study director or laboratory management. The attached page from the report on this study indicates that the study was conducted under FDA Good Laboratory Practice Regulations (21 CFR 58).

GOOD LABORATORY PRACTICE STATEMENT

This study does not meet the requirements for 40 CFR Part 160 (see above).

Submitter/Sponsor of Study:

Merrill Tisdel
Agricultural Division
CIBA-GEIGY Corporation
Greensboro, North Carolina

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Failure of the lung to collapse was observed in one test rat.

Under the conditions stated in this report, the LC_{50} for CGA-41065 Technical in acetone is less than the analytical concentration of 2.13 mg/l.

J. Michael Morgan 11-12-81

J. Michael Morgan, Ph.D. Date
Study Director

All work relating to this study was done in conformity with the FDA - Good Laboratory Practice Regulations (21 CFR 58).

The study was inspected by a Quality Assurance Specialist on the dates shown below. Management, including the Study Director, was informed of the results of these inspections on the dates shown if any problems were found.

The data in the report were compared with the raw data and are in agreement. The report and study file were examined to assure that if any problems were found during Quality Assurance inspections they were corrected and, if necessary, their effect on the study documented.

1. On-site Inspection - conducted October 16, 1981.

2. Interim Inspection - conducted October 28, 1981.

3. Final Data Inspection and Report Audit - conducted November 9 and 10, 1981; reported to Management, including the Study Director, November 10, 1981.

Bernard R. Szyszko 11/12/81

Bernard R. Szyszko, B.A., M.T. Date
Supervisor, Quality Assurance

The raw data relating to this study are stored at ToxiGenics, Inc. Storage is as per FDA GLP's and may include volume reduction by conversion to certified microform.

Date of Report: November 12, 1981

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Certification of Availability of Raw Data

I hereby certify that the submitter possesses or has access to the raw data used in or generated by the study summarized in this document.

Submitter's Representative:

Signature/Date: Merrill Tisdel

Typed Name: Merrill Tisdel

Title: Toxicologist

Certification of Accuracy of Summary and Adequacy of the Study

I certify, in compliance with FIFRA section 4(e)(1)(A), that this summary accurately represents the data presented in the report(s) of this study cited by MRID, and that this study fully satisfies all pertinent requirements of the OPP Guideline it addresses.

Submitter's Representative:

Signature/Date: Merrill Tisdel

Typed Name: Merrill Tisdel

Title: Toxicologist

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81-3 Acute Inhalation Toxicity in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1. Y — Technical form of the active ingredient tested. (for reregistration only)
2. Y — Product is a gas, a solid which may produce a significant vapor hazard based on toxicity and expected use or contains particles of inhalable size for man (aerodynamic diameter 15 um or less).
3. *Y — At least 5 young adult rats/sex/group
4. *Y — Dosing, at least 4 hours by inhalation.
5. *Y/N — Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content.
6. Y/N — Chamber temperature, 22° C (±2°), relative humidity 40-60%.
7. Y — Monitor rate of air flow
8. Y — Monitor actual concentrations of test material in breathing zone.
9. Y — Monitor aerodynamic particle size for aerosols.
10. N — Doses tested, sufficient to determine a toxicity catagory or a limit dose (5 mg/L actual concentration of respirable substance).
11. Y — Individual observations at least once a day.
12. Y — Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.
13. Y — Individual daily observations.
14. *Y — Individual body weights.
15. *Y — Gross necropsy on all animals.

Criteria marked with a * are supplemental and may not be required for every study.

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IDENTIFICATION OF TEST MATERIAL

Chemical Name

CAS Name: N-(2-Chloro-6-fluorobenzyl)-N-ethyl-α,α,α,-trifluoro-2,6-dinitro-p-toluidine

or

2-Chloro-N-[2,6-dinitro-4-(trifluoromethyl)phenyl]-N-ethyl-6-fluorobenzenemethanamine

Common Name: Flumetralin

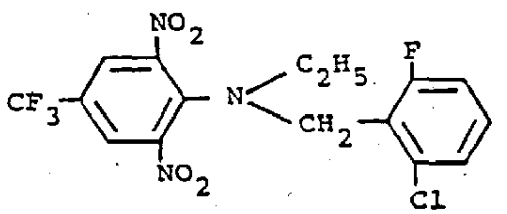
Trade Name: Prime +®

CIBA-GEIGY Code Number: CGA-41065

CAS Registry Number: 62924-70-3

EPA Shaughnessy Number: Unknown

Chemical Structure:



Percent Active Ingredient

92% minimum

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Flumetralin: 81-3: Acute Inhalation Toxicity in the Rat

1. The test article was Flumetralin (CGA-41065) Technical, a bright orange crystalline substance, FL-810824, purity 94.1%. The test article was dissolved in acetone (ACS grade) as a vehicle (50% w/w).

2. In this study, when the test material was generated as an aerosol, it contained particles of inhalable size for humans, i.e., less than 15 µm.

3. Five male and five female albino rats (CRL:CD(SD)BR) were tested at one test dose level. A second group of five male and five female rats was tested concurrently as a vehicle control group, and a third group of five male and five female rats was tested concurrently as an untreated control group.

4. The duration of exposure was four continuous hours for each inhalation exposure group.

5. The dynamic air flow through the exposure chambers provided approximately 2.4, 4.4, and 6.7 air changes per hour for the test, vehicle control, and untreated control groups, respectively. Oxygen content was not assessed.

6. Chamber temperatures were assessed every 30 minutes during the exposure periods for the test, vehicle control, and untreated control groups. For the test group, chamber temperature ranged from 22.2 to 23.3°C. For the vehicle control group, chamber temperature ranged from 22.8 to 23.3°C. For the untreated control group, temperature ranged from 22.8 to 23.9°C. Relative humidity for the untreated control inhalation exposure ranged from 28% to 58%. Relative humidity for the test and vehicle control exposures was not assessed.

7. Air flow in each test chamber was 20.4 liters/minute for the test group, 36.9 liters/minute for the vehicle control group, and 55.5 liters/minute for the untreated control group.

8. The analytical concentration of the both the test material and the vehicle in the breathing zone of the exposure atmosphere of the test group was assessed nine times during the exposure period. The time-weighted average concentration of

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Flumetralin Technical was 2.13 mg/l. The time-weighted average concentration of acetone was 8.52 mg/l. The analytical concentration of the vehicle in the vehicle control sequence was assessed every four minutes during the exposure period. The time-weighted average concentration of acetone was 11.38 mg/l.

9.

Concentration (mg/l)	Mass Median Diameter	Geometric Standard Deviation	Percent Less Than/Equal to 1.0 micron
2.13	1.76, 1.36[a]	2.01, 1.55[a]	20.8, 19.2[a]

[a]Two samples for each parameter.

10.

Group	Number Dead/Number Treated		
	Males	Females	Overall
Test	1/5	1/5	2/10
Vehicle Control	0/5	0/5	0/10
Untreated Control	0/5	0/5	0/10
Test Article LC_{50} (mg/l)	>2.13	>2.13	>2.13

11. Observations for pharmacological and/or toxicological effects and mortality were recorded at least every 15 minutes during the first hour of exposure and at least every 30 minutes for the remaining three hours. Observations of poor coat quality, yellow/brown stained fur, lacrimation, salivation, and irregular breathing were noted in test group animals on the day of exposure. No reactions were observed in vehicle or untreated control animals.

12. Individual observations were made at least twice daily for 14 days following the exposure period. Animals in the test group exhibited yellow/brown stained fur, irregular breathing, and crusty nose.

13. See Items 11 and 12.

14.

Group	Body Weights (g) (Mean/Number Alive)					
	Males			Females		
	Initial	Day 7	Day 14	Initial	Day 7	Day 14
Test	245/5	272/4	334/4	216/5	222/4	239/4
Vehicle Control	253/5	309/5	356/5	226/5	241/5	260/5
Untreated Control	249/5	299/5	346/5	207/5	216/5	232/5

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15. A gross necropsy examination was conducted on the two animals which died during the study and all surviving animals at study termination. No treatment-related abnormalities were observed in any animal in any group.

16. There were no significant changes from the Acceptance Criteria in this study. Four deviations from the Acceptance Criteria are noted. Under Item 5, there were fewer than ten air changes per hour in the three exposure sequences, and the oxygen content was not assessed. Under Item 6, relative humidity was not measured for the test or vehicle control groups. These deviations are considered to be insignificant because there were no indications that the correct bioloading for the chambers had been exceeded. The air flow was adequate for the chamber size and limited number of animals, as evidenced by negligible rise in temperature in each of the three exposure sequences. Under Item 10, the limit dose, 5 mg/l, was not tested. Current guidelines call for particle size distribution of 25% less than 1 µm. If this is not achievable, then testing at 5 mg/l is required. In this study, approximately 20% of the particles were ≤1 µm, and 50% ≤2 µm at 2.13 mg/l. Because the LC_{50} in this study was >2.13 mg/l and there were no significant toxicological findings, it is unlikely that increasing the number of particles ≤1 µm from 20% to 25% would significantly change the LC_{50}, nor would it require a Category II label rather than the current Category III label. For this reason, this deviation is not considered to be significant.

GILLIS:R503SW0921JG/MT

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